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EXAMINER	
CARTER, KENDRA D	

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1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/523,455	ENGEL ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9 and 16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of December 20, 2007 made to the office action filed June 20, 2007. Claims 1, 4-9 and 16-25 are pending. Claims 1, 4-9 and 16-25 are amended.

For the reasons in the previous office action and below, the Applicant's arguments of the following rejections were found not persuasive and thus upheld: 1) the 35 U.S.C. 103(a) rejection of claims 1, 4, 5, 7, 16, 18, 21 and 25 as being unpatentable over Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al. in view of Ziegler et al., in further view of Hall et al.; 2) the 35 U.S.C. 103(a) rejection of claims 22-24 as being unpatentable over Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al. in view of Ziegler et al., in further view of Hall et al. as applied to claims 1, 4, 5, 7, 16, 18, 21 and 25 above, and further in view of Garfield et al.; 3) the 35 U.S.C. 103(a) rejection of claims 6, 8, 9, 17, 19 and 20 as being unpatentable over Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al. in view of Ziegler et al., in further view of Hall et al. as applied to claims 1, 4, 5, 7, 16, 18, 21 and 25 above, and further in view of Deghengi et al. or Rabasseda et al.; 4) the obviousness-type double patenting rejection of claims 1, 4-9, 16-21 and 25 as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 in view of Ziegler et al., Hall et al., Deghengi, Rabasseda et al. and Kent.

Due to the amendment to the claims, the modified 35 U.S.C. 103(a) and obviousness double patenting rejections are made below.

The Applicant's arguments are addressed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 1, 4, 5, 7, 16, 18, 21 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over (i) the article by Felberbaum et al. (or record) or Albano et al. (of record) or Engel et al (of record) or the article entitled "The Single or Dual Administration of the Gonadotropin-releasing Hormone Antagonist Cetrorelix in an In Vitro Fertilization-Embryo Transfer Program" by Olivennes et al, 1994, in view of (ii) the article entitled "Synchronization of Endogenous and Exogenous FSH Stimuli in Controlled Ovarian Hyperstimulation (COH)" by Ziegler et al, 1998, and further in view of (iii) the article entitled "Variable Tolerance of the Developing Follicle and Corpus Luteum to Gonadotropin-Releasing Hormone Antagonist-Induced Gonadotropin Withdrawal in the Human" by Hall et al.

Felberbaum et al. teaches that GnRH antagonists such as Cetrorelix and Ganirelix can be administered in an IVF program to avoid premature LH-surges (see summary, in particular.) Felberbaum et al. teaches that patients are treated with HMG starting on day 2 (see summary, in particular), and thus teaches programming controlled stimulation of ovarian follicle growth as in part (c). Felberbaum et al. teaches that the patients are administered cetrorelix from day 7 until induction of ovulation with HCG, and thus teaches suppression of premature ovulation by administering the LHRH-antagonist during the follicular cycle as in part (d), and induction of ovulation with HCG as in part (e) (see summary, in particular.) Felberbaum et al. also teaches performing IVF, as in part (f), and also as in claim 25 (see summary in particular.) Thus, Felberbaum et al. teaches a method for programming an infertility treatment cycle having steps (c)-(f) as recited in claim 1.

Albano et al. teaches a method for assisted reproduction in which an ovarian stimulation protocol is used (see abstract, in particular.) Albano teaches that the ovarian stimulation method involved administration of HMG during day 2 of the menstrual cycle and administration of the gonadotrophin-releasing hormone antagonist cetrorelix (LHRH antagonist) on day 6 of the menstrual cycle (follicular phase) (see abstract, in particular), and thus teaches steps (c) and (d) of the method. Albano et al. further teaches that ovulation is induced with HCG (see abstract, in particular), and thus teaches step (e). Albano et al. teaches the steps can be performed in a method of in-vitro fertilization (see introduction, in particular), and thus teaches step (f) and claim 25.

Thus, Albano et al. teaches a method for programming an infertility treatment cycle having steps (c)-(f) as recited in claim 1.

Engel et al. teaches the treatment of fertility disorders by administering HMG to hyperstimulate the ovaries (see column 1, lines 10-25, in particular), as in step (c) administering an LHRH antagonist such as cetrorelix during the follicular phase, to reduce premature LH surges during stimulated cycles (see column 2, lines 1-15, in particular), as in step (d), and inducing ovulation with HCG (see column 1, lines 55-60, in particular), as in step (e). Engel et al. teaches that the method can be used in an assisted reproduction technique (see column 3, lines 15-40, in particular; addresses step (f).) Thus, Engel et al. teaches a method for programming an infertility treatment cycle having steps (c)-(f) as recited in claim 1.

Olivennes et al. teaches providing a GnRH antagonist such as cetrorelix to prevent premature LH surges in an IVF-ET program (see abstract, in particular.) Olivennes et al. teaches that controlled ovarian hyperstimulation (COH) is carried out with hMG on day 2 of the menstrual cycle, with cetrorelix being administered during the hyperstimulation (follicular phase) (see abstract, in particular.) Olivennes et al. teaches that ovulation is triggered by administration of HCG (see paragraph bridging pages 469-470, in particular.) Thus, Olivennes et al. a method for programming an infertility treatment cycle having steps (c)-(f) as recited in claim 1.

The references do not specifically teach programming the start of a programmed menstrual cycle by inducing luteal regression comprising administering a LHRH antagonist during the luteal phase of the preceding menstrual cycle (claim 1a); terminating administration of the LHRH antagonist prior to the onset of menses (claim 1b); wherein the programmed menstrual cycle is programmed on a day that permits the assisted reproduction techniques to be carried out during routine operations of laboratories, clinics, or other assisted reproduction facilities (claim 4), or the specific amounts of the LHRH antagonist (claim 1a).

Ziegler et al. teaches the desirability of permitted advanced timing of the onset of controlled ovarian hyperstimulation (COH) (see page 561, right hand column, in particular.) Ziegler et al. teaches that it is difficult to properly time the onset of HMG administration (see introduction, in particular.) Ziegler et al: teaches that treatments were devised to improve scheduling of treatments for patients and team members by synchronizing FSH rises that initiate new menstrual cycles with the onset of HMG administration for COH (see page 563, left hand column, in particular.) Ziegler et al. teaches that oestradiol was used for timing the follicular phase increase in FSH to provide for the onset of HMG treatment (see discussion, first full paragraph, in particular), and further teaches that advanced programming of COH has been previously achieved with oral contraceptives (see paragraph bridging pages 563-564, in particular.) Ziegler et al. teaches that the oestradiol treatment was started 7.1 days before the onset of menses (luteal phase) and continued for 5 days thereafter (see

results section, in particular.) Thus, Ziegler et al. teaches the desirability of permitting the advanced timing of COH treatments by starting the administration of a composition during the luteal phase to allow for advanced scheduling of treatments.

Hall et al. teaches that administration of a GnRH antagonist (LHRH antagonist) in the mid-luteal phase results in luteolysis (see abstract, in particular.) Hall et al. teaches that three daily antagonist injections begun on day 4 or 5 after ovulation (luteal phase) resulted in menstrual bleeding within 24-48 hrs of the final day of the antagonist administration (see page 997, MLP studies, left hand paragraph, in particular.) Thus, Hall et al. teaches terminating administration of the LHRH antagonist prior to the onset of menses (claim 1b), administration of an LHRH antagonist during the luteal phase of the preceding menstrual cycle (claim 1a), and a programmed menstrual cycle (claim 1a). Hall et al. teaches that seventy two hours of gonadotropin deprivation (due to GnRH antagonist administration) in the luteal phase resulted in prompt tuteolysis in all subjects (see page 998, final paragraph, in particular.) Hall et al. further teaches that in human studies, complete luteolysis is demonstrated in response to GNRH antagonism (see page 999, left hand column first full paragraph, in particular.) Thus, Hall et al. teaches that administration of a GnRH antagonist during the luteal phase results in luteolysis and shortening of the luteal phase (addressing claim 1a).

Hall et al. does not specifically teach providing an LHRH antagonist that is selected from the group of cetrorelix, teverelix, ganirelix, antide and abavelix. However, as discussed above, Felberbaum et al, Albano et al, Engel et al. and Olivennes et al. teach that cetrorelix is a GnRH antagonists (LHRH antagonist) suitable for administration. Felberbaum et al. teaches that garnirelix is suitable for administration. Accordingly, it would have been obvious to provide cetrorelix or garnirelix as the GnRH antagonist in the method of Hall et al. with the expectation of providing a suitable GnRh antagonist.

Regarding the specific amount of antagonist administered as disclosed in claim 1(a), Hall et al. teaches administering 150 micrograms/kg (see abstract, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of antagonist provided in the method, according to the guidance provided by Hall et al, to provide the desired rate and extent of luteolysis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide advanced timing as taught by Ziegler et al. with the assisted reproductive techniques involving administration of HMG and ovarian

stimulation such as COH of Felberbaum et al, Albano et al, Engel et al. and Olivennes et al, because the references teach assisted reproductive techniques involving stimulation with HMG prior to induction of ovulation with HCG, whereas Ziegler et al. teaches that a COH treatment involving HMG ovarian stimulation can be improved by providing advanced timing via administration of a composition to allow for improved scheduling of treatments. Thus, one of ordinary skill in the art would have found it obvious to combine the advanced timing method with the assisted reproductive techniques of Felberbaum et al, Albano et al, Engel et al. and Olivennes et al with the expectation of improving the efficiency of treatment scheduling and thus fertilization success with the advanced timing method.

Accordingly, one of ordinary skill in the art would have found it obvious to provide the GnRH antagonist (LHRH antagonist) of Hall et al. in the advanced timing method of assisted reproductive techniques of Felberbaum et al, Albano et al, Engel et al, Olivennes et al. and Ziegler et al, because Ziegler et al. teaches the desirability of providing controlled timing to allow for better scheduling of procedures and thus better effectiveness of the procedures, such as by controlling the menstrual cycle via oral contraceptives, whereas Hall et al. teaches compositions that control the length and duration of the menstrual cycle, to increase the rate of luteolysis and decrease the duration of the luteal phase. Thus, one of ordinary skill in the art would have found it obvious to provide the composition Hall et al, in the method of Felberbaum et al, Albano et al, Engel et al, Olivennes et al. and Ziegler et al, with the expectation of providing

control of the menstrual phases to provide advanced timing for the assisted reproductive techniques. Thus claim 1 is obvious over the recited references.

Regarding claim 4, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the days on which the compositions are provided, according to the guidance provided by the references, to provide the advanced timing and scheduling of the assisted reproductive techniques. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955.)

Regarding claims 5 and 16, the references teach providing cetrorelix as the antagonist during the luteal phase as well as during ovarian stimulation, as discussed above.

Regarding claims 7 and 18, Felberbaum et al. teaches administration of ganirelix as a GnRH antagonist, as discussed above.

Regarding claim 21, the references teach ovarian stimulation with HMG, as discussed above.

(2) Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over (i) the article by Felberbaum et al. (or record) or Albano et al. (of record) or

Engel et al (of record) or the article entitled "The Single or Dual Administration of the Gonadotropin- releasing Hormone Antagonist Cetrorelix in an In Vitro Fertilization-Embryo Transfer Program" by Olivennes et al, 1994, in view of (ii) the article entitled "Synchronization of Endogenous and Exogenous FSH Stimuli in Controlled Ovarian Hyperstimulation (COH)" by Ziegler et al, 1998, and further in view of (iii) the article entitled "Variable Tolerance of the Developing Follicle and Corpus Luteum to Gonadotropin-Releasing Hormone Antagonist-Induced Gonadotropin Withdrawal in the Human" by Hall et al, as applied to claims 1,4-5, 7, 16, 18, 21 and 25 above, and further in view of U.S. Patent No. 5,470,847 to Garfield et al (of record).

Felberbaum et al, Albano et al, Engel et al, Olivennes et al, Ziegler et al. and Hall et al. are applied as discussed above, and teach assisted reproductive techniques involving a step of inducing ovulation with HMG (a gonadotropin), as discussed above. The references do not specifically teach inducing ovulation with the particular compounds that are clomiphene, a combination of antioestrogens and gonadoptropins or a combination of clomiphene with gonadotropins, as in claims 22-24.

Garfield et al. teaches that clomiphene is a non-steroidal antiestrogen that stimulates ovulation by stimulating follicle growth and maturation (see column 3, lines 9-20, in particular.)

Accordingly, it is considered that one of ordinary skill in the art would have found it obvious to incorporate clomiphene into the assisted reproductive techniques as discussed by the references, either alone or in combination with a gonadotropin such as HMG, because Garfield et al. teaches that clomiphene is an antiestrogen that stimulates follicle growth and ovulation, whereas the Felberbaum et al, Albano et al, Engel et al, Olivennes et al. and Hall et al. references teach that HCG (a gonadotropin) is provided to induce ovulation, as discussed above. Thus, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine the clomiphene with the above-described assisted reproductive techniques using the gonadotropin HCG with the expectation of providing suitable stimulation and induction of ovulation for the assisted reproductive techniques.

(3) Claims 6, 8-9, 17 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over (i) the article by Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al, and (ii) Ziegler et al, in view of (iii) Hall et al, as applied to claims 1,4-5, 7, 16, 18, 21 and 25 above, and further in view of (iv) UIS. Patent No. 5,945,128to Deghengi et al (of record) or Rabasseda et al (of record.)

Felberbaum et al, Albano et al, Engel et al, Olivennes et al, Ziegler et al. and Hall et al. are applied as discussed above, and teach providing a GnRH antagonist (LHRH antagonist) such as cetrorelix or ganirelix in the therapeutic fertility management

technique as recited in claim 1. The references do not specifically teach providing teverelix, antide or abavelix, as recited in claims 6, 8-9, 17 and 19-20.

Dehgenghi teaches that cetrorelix, teverelix, ganirelix and antide are known to be LHRH antagonists (GnRH antagonists) (see column 2, lines 19-23, in particular.) Rabasseda et al teaches that LHRH-antagonists (GnRH antagonists) such as cetrorelix, ganirelix and abarelix are known to be useful in the treatment of female infertility (see introduction and Table 1 of page 397, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the antagonists of Deghenghi or Rabasseda et al. in the method of Felberbaum et al, Albano et al, Engel et al, Olivennes et al, Ziegler et al. and Hall et al, with the expectation of providing a suitable GnRH antagonist (LHRH antagonist) in the method. Furthermore, regarding the specific amount of the antagonist provided, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of the antagonist provided in the method, according to the guidance provided by the references, to provide the desired advanced timing and/or ovulation control. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955.)

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 4-9, 16-21 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 to Engel et al. in view of the Ziegler et al, Hall et al, Dhegenghi, Rabasseda et al and Kent (4,016,259 of record) references as applied above.

The instant claims differ from those in the patented case because the patented case only recites providing an LHRH- antagonist with stimulation of ovarian follicle growth, ovulation induction and intrauterine insemination, whereas the instant case

further recites a programming step involving the LHRH antagonist or a progestogen composition.

However, the combination of such a programming method with an infertility treatment is obvious over the teachings of Ziegler et al, Hall et al, Dhegenghi, and Rabasseda et al. as discussed for claims 1 and 4-9, 16-21 and 25 in the 103(a) rejection made above. Kent discloses that the combination of progestogens and estrogen, i.e., mestranol and ethinylestradiol is useful in animal contraception (see col.1 lines 20-25). Accordingly, the instant claims are not patentably distinct from those in the patented case.

Response to Arguments

Applicant's arguments filed December 20, 2007 have been fully considered but they are not persuasive.

The 35 U.S.C. 103(a) rejections of claims 1, 4, 5, 7, 16, 18, 21 and 25

> The Applicant argues that the examiner failed to make a primafacia case of obviousness because the factual inquiries set forth in *Graham v John Deere Co.* have not been considered, and none of the rationales identified by the U.S. Supreme Court in KSR apply.

The Examiner disagrees because the each teaching of the prior art has been provided to give the scope, contents and level of ordinary skill in the art regarding programming an infertility treatment. Additionally, the differences between the prior art and claims have been addresses, as well as an explanation of why the claims are obvious over the prior art. Thus, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), have been addressed. In regards to the obviousness to combine the prior art references, such as a specific suggestion or teaching in the two references, the KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision EX parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). Thus, the Examiner's above rationales identify with KSR.

> The Applicant argues that the Examiner has not addressed the predictability in the art and/or a reasonable expectation of success from the teachings of the cited references. Additionally, the prior art does not address the amended claims.

The Examiner disagrees because the reasonable expectation of success of one of ordinary skill in the art was provided by the Examiner. Particularly, one of ordinary skill in the art would have found it obvious to provide the composition Hall et al, in the method of Felberbaum et al, Albano et al, Engel et al, Olivennes et al. and Ziegler et al, with the expectation of providing control of the menstrual phases to provide advanced

timing for the assisted reproductive techniques. Additionally, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine the clomiphene with the above-described assisted reproductive techniques using the gonadotropin HCG with the expectation of providing suitable stimulation and induction of ovulation for the assisted reproductive techniques. The limitations in the amended claims have been addressed above.

> The Applicant argues that Ziegler et al. fails to remedy the deficiencies of the primary references. Ziegler et al. fails to teach or suggest an "advanced timing method" by administration of LHRH antagonists in the preceding menstrual cycle; or termination of administration of an LHRH antagonist or administration of the "advanced timing compound" prior of the onset of menses. Additionally, Ziegler et al. teaches away from the instantly claimed method by teaching that their approach provides the advantage of permitting advance timing of the onset of COH treatments "provides the practical advantage of permitting an advanced timing of the onset of COH treatments when gonadotrophin-releasing hormone agonists are not used" (see page 11 of Remarks submitted on December 20, 2007.)

The Examiner disagrees, and notes that Ziegler et al. does not expressly teach away from the use of LHRH antagonists for controlling the onset of COH treatments. Furthermore, as Ziegler et al. generally teaches the desirability of permitting advanced timing for the onset of COH treatments to allow for better scheduling, it is considered that the reference as a whole teaches the desirability of incorporating agents and methods capable of providing the desired advanced timing. The Examiner notes that the Ziegler et al. reference is being used to teach the desirability of controlling the timing of the onset of treatment in order to allow better

scheduling of procedures, as has been discussed above. The Examiner further notes that the Ziegler et al. reference is also being applied for it's teaching of the general desirability of controlling the timing of the techniques, for example by providing contraceptives. Ziegler et al. therefore provides motivation to those of ordinary skill in the art to provide controlled timing of the treatment cycle in order to allow better scheduling. The Examiner notes that the Hall et al. reference is being applied to teach that the menstrual cycle can be controlled with GnRH antagonists (which shorten the menstrual cycle.) Hall et al. additionally provides the teachings of administering an LHRH antagonists in the preceding menstrual cycle, and termination of administration of an LHRH antagonist prior of the onset of menses.

> The Applicant argues that Hall et al. teaches away from the instant invention because patients with LHRH antagonists in mid-follicular phase resulted in a prolongation of follicular phase length by 9 days (see page 995, right hand column). Thus, one of ordinary skill in the art would conclude that administration of an LHRH antagonist during the luteal phase results in a disturbance in hormones and endocrine regulation system that would not only fail to promote COS/ART programming, but would be counterproductive.

The Examiner disagrees because the claims are drawn to administration of the LHRH antagonist during the luteal phase, in which Hall teaches by administering three daily antagonist injections on day 4 or 5 after ovulation (luteal phase). Additionally Hall teaches that complete luteolysis is demonstrated in response to the LHRH antagonist (see page 999, left hand column, first full paragraph).

> The Applicant argues that one of ordinary skill in the art would not have been motivated to provide the LHRH antagonists in the claimed method because they were considered to interfere with mechanisms involved in germinal vesicle breakdown and cell signaling pathway driving the oocyte into meta phase II, and with other general mechanisms (Applicants cite a number of references that supposedly show this state of the art; see page 12, first full paragraph of Remarks submitted December 20, 2007.) The Examiner respectfully disagrees with this assertion. To the contrary to the Examiner's response, none of the cited references demonstrate safe and effective use when LHRH antagonists are administered in the luteal phase of the preceding menstrual cycle.

The Examiner disagrees for reasons stated in the previous office action. Particularly, Felberbaum et al, Albano et al, Engel et al and Oliveness et al. references all teach GnRH or LHRH antagonists that are safe and effective for use with assisted reproductive techniques, whereas the Hall et al. reference teaches that GnRH antagonist shorten the luteal phase of the menstrual cycle, thus rendering it obvious to combine with a method such as that in Ziegler to provide timing of menstrual cycles for assisted reproductive techniques. It is the combination of the references that teach the motivation of when the LHRH antagonist is administered but the primary references and Hall teach effective administration of LHRH antagonist for the common purpose of assisted reproductive techniques.

The 35 U.S.C. 103(a) rejections of claims 6, 8, 9, 17, 19 and 20

> Applicant argues that both Deghengi and Rabasseda, viewed either alone or in combination, fail to remedy the deficiencies of the primary references as discussed above.

The Examiner disagrees because Deghengi and Rabasseda are used as a reference to teach that cetrorelix, teverelix, ganirelix and antide are known to be LHRH antagonists (GnRH antagonists) and that LHRH-antagonists (GnRH antagonists) such as cetrorelix, ganirelix and abarelix are known to be useful in the treatment of female infertility. The arguments in respect to the primary references have been addressed above.

The Obviousness-Type Double Patenting rejection of claims 1, 4-9, 16-21 and 25

> Applicants argues that the '192 patent does not teach the amended claims, and as discussed previously, at the time of filing, one of ordinary skill in the art would expect that performing the claimed methods would have deleterious effects that are both incompatible and counterproductive to programming COS/ART procedures and thus withdrawal of the rejection is respectfully requested.

The Examiner disagrees because the amended limitations are addressed by the teachings of Hall et al. Particularly, Hall et al. teaches that three daily antagonist injections begun on day 4 or 5 after ovulation (luteal phase) resulted in menstrual bleeding within 24-48 hrs of the final day of the antagonist administration (see page 997, MLP studies, left hand paragraph, in particular.) Thus, Hall et al. teaches terminating administration of the LHRH antagonist prior to the onset of menses (claim 1b), administration of an LHRH antagonist during the luteal phase of the preceding menstrual cycle (claim 1a), and a programmed menstrual cycle (claim 1a). Additionally, as stated above, Felberbaum et al, Albano et al, Engel et al and Oliveness et al. references all teach GnRH or LHRH antagonists that are safe and effective for use

with assisted reproductive techniques, whereas the Hall et al. reference teaches that GnRH antagonist shorten the luteal phase of the menstrual cycle, thus rendering it obvious to combine with a method such as that in Ziegler to provide timing of menstrual cycles for assisted reproductive techniques. It is the combination of the references that teach the motivation of when the LHRH antagonist is administered but the primary references and Hall et al. that teach effective administration of LHRH antagonist for the common purpose of assisted reproductive techniques.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. D. C./
Examiner, Art Unit 1617

Claims 1 and 3-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engel et al. (EP 0788 799, of record) and Albano et al. (of record) and Felberbaum et al. (of record) and Garfield (5,470,847, of record) in view of Deghenghi (5,945,128, of record) and Rabasseda et al. (of record) and Kent (4,016,259 of record) for reasons of record stated in the Office Action dated May 7, 2002 in Paper No. 10.

Engel et al. discloses that an LHRH-antagonist, such as cetrorelix, is useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., ICSI or intrauterine insemination by sperm injection, with multiple follicle and oocyte development. See the abstract, col. 1 lines 10-20, 30-34, 39-59, col. 2 lines 1-13, 16-25, col.3 lines 1-12, and claims 1-14. Engel et al. also discloses exogeneous stimulation of the ovarian follicle growth and ovulation induction with HCG, LHRH, or LHRH-agonists and the stimulation is performed by administration of FSH or HMG with or without recombinant LH. See Abstract, col. 2 lines 38-43. Engel et al. further discloses the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Examples

claim 6-8. Finally, Engel et al. teaches progesterone is useful in supporting the beginning of pregnancy. See col.1 lines 23-24.

Albano et al. teaches that LHRH-antagonists, such as cetrorelix, are useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., IVF and ICSI, with multiple follicle and oocyte development, as well as the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Abstract, Introduction and Results. Albano et al. further teaches that progesterone concentration is significantly lowered due to the administration of cetrorelix. See page 2115, 5th paragraph of right column.

Felberbaum et al. teaches that LHRH-antagonists, such as cetrorelix and ganirelix, are useful in the method of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques, e.g., IVF and ICSI, with multiple follicle and oocyte development, as well as the effective amount of the LHRH-antagonist cetrorelix within the instant claim to be administered during luteal phase. See Abstract, page 399-402 Felberbaum et al. further teaches a fall of sex steroids due to the administration of LHRH-antagonists. See page 398, the last three lines.

Garfield teaches that the administration of progestogen in the follicular phase is useful along with other progestins, an estrogen, e.g. ethinylestradiol, and an LHRH-antagonist in a method of controlling ovarian stimulation and preventing conception. See abstract, col.1 lines 18-67 and col.5 lines 35-38. Garfield also teaches that the

ovarian stimulation is achieved with antioestrogens, such as clomiphene, combined with gonadotropins. See col. 2 lines 9-17, col.5 lines 64-67 and col.6 lines 30-40.

The prior art does not expressly disclose that the particular LHRH-antagonist are teverelix, antide, and abarelix and their effective amounts to be administered. The prior art does also not expressly disclose that the ovarian stimulation therapy may be on Fridays to Mondays, and ooctye pick up and ART may be undertaken on Mondays to Thursdays. The prior art does not expressly further disclose the particular employment of oral contraceptive preparations containing progestogen and mestranol in the management of infertility.

Deghenghi discloses cetrorelix, teverelix, ganirelix and antide are known to be LHRH-antagonists. see col.2 lines 19-23.

Rabasseda et al. teach that LHRH-antagonists such as cetrorelix, ganirelix, and abarelix are known to be useful in the treatment of female infertility (see Introduction and Table 1 of page 397).

Kent discloses that the combination of progestogens and estrogen, i.e., mestranol and ethinylestradiol is useful in animal contraception (see col.1 lines 20-25).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular LHRH-antagonist such as teverelix, antide, and abarelix and to optimize their effective amounts to be administered, and to schedule or program the ovarian stimulation therapy on Fridays to Mondays and ooctye pick up and ART on Mondays to Thursdays, to employ the particular estrogen, mestranol, in oral contraceptive preparations along with progestogen.

One having ordinary skill in the art would have been motivated to employ the particular LHRH-antagonist such as teverelix, antide, and abarelix since teverelix, antide, and abarelix are known to be LHRH-antagonists, useful in the methods of controlled ovarian situmlation and assisted reproductive techniques and of the treatment of infertility according to Engel et al., Albano et al., Felberbaum et al., Deghenghi and Rabasseda et al. Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the optimization of amounts of active agents to be administered is considered well within the skill of artisan. One having ordinary skill in the art would have been motivated to schedule or program the ovarian stimulation therapy on Fridays to Mondays and ooctye pick up and ART on Mondays to Thursdays since scheduling or programming the known ovarian stimulation therapy for Fridays to Mondays according to the calendar is considered well within the skill of artisan as the optimization of a result effective parameter, e.g., dosage regimen. One having ordinary skill in the art would have been further motivated to employ the particular estrogen, mestranol, in oral contraceptive preparations along with progestogen in the management of infertility since the known contraceptive preparations of Kent contain mestranol and progestogen, and estrogen and progestin containing contraceptive agents are known broadly to be useful in the therapeutic management of infertility.

Since all method and composition components herein are known to be useful to treat or manage the infertility, it is considered prima facie obvious to combine them into

a single method useful for the very same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Applicant's remarks filed on May 19, 2003 in Paper No. 17 with respect to this rejection of claims 1 and 3-24 made under 35 U.S.C. 103(a) have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Again, Applicant's arguments that the cited references, either alone or in combination does not render the presently claimed invention unpatentable have been considered but are not found persuasive.

Applicant asserts the citation of seven different and unrelated documents. Contrary to Applicant's assertion, all cited references, especially all primary references, Engel et al., Albano et al., Felberbaum et al. and Garfield, clearly disclose the methods of suppression of premature ovulation in controlled ovarian sitmulation and assisted reproductive techniques.

As discussed in the Final Rejection, the instant LHRH-antagonists such as teverelix, antide, and abarelix are known to be LHRH-antagonists and known to be useful in the methods of controlled ovarian situmlation and assisted reproductive techniques and of the treatment of infertility according to Engel et al., Albano et al., Felberbaum et al., Deghenghi and Rabasseda et al. Thus, each step in the instant claimed method is known in the prior art. It must be recognized that any judgment on

obviousness takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made. See MPEP 2145.

Further, the particular estrogen herein, mestranol, in oral contraceptive preparations in combination with progestogen are well known contraceptive agents and also known broadly to be useful in the therapeutic management of infertility according to the prior art. Therefore, one of ordinary skill in the art would have reasonably expected that combining these particular agents known useful for the same purpose in a composition to be administered would produce additive therapeutic effects to improve the treatment of in the therapeutic management of infertility, absent evidence to the contrary.

Since all active composition components herein are known to useful in the therapeutic management of infertility, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected based on the well settled principle set forth *In re Kerkhoven* regarding combination inventions. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Applicant's results of the instant method (program) in the specification at page 4-5 herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art but are not deemed persuasive for the reasons below. The results provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art since there is no side-by-side comparison with the closest prior art. Therefore, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of therapeutic management of infertility by intrauterine insemination consisting of substantially similar method steps and administering the same pharmaceutical agents, i.e. an LHRRH-antagonist such as cetrorelix, HCG, native LHRH, LHRH-agonists or recombinant LH.

The claims of the instant application is drawn to the method of therapeutic management of infertility by programming of controlled ovarian stimulation and assisted reproductive procedures the improvement.

One having ordinary skill in the art would clearly recognize that the method in the patent and the method in the instant application consisting of substantially similar method steps and administering the same pharmaceutical agents are seen to substantially overlap.

Thus, the instant claims 1 and 3-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER, whose telephone number is (571)272-9034. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0629.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
September 29, 2003